

**Trabalho Final do Mestrado Integrado em Medicina**

**Miliary Tuberculosis in an Immunosuppressed Patient  
With Crohn's Disease**

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**Case Report and Systematic Review of the Literature**

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## **ABSTRACT**

Crohn's disease (CD) is an idiopathic inflammatory bowel disease (IBD) characterized by an inappropriate inflammatory response. Biological therapies directed at specific inflammatory mediators revolutionized the treatment but leave the patient more susceptible to infection by inducing a certain extent of immunosuppression. This includes both general infections with common agents and more specific complications such as tuberculosis (TB). We present a patient with IBD who, despite negative TB screening, developed an opportunistic miliary tuberculosis infection while treated with double immunosuppressive therapy (azathioprine and infliximab) for refractory Crohn's disease. He presented with fever, weight loss, elevated transaminases, coagulopathy, anemia and neutropenia. Comprehensive diagnostics including computer tomography (CT) scan, bronchoscopy and liver biopsy revealed the diagnosis of miliary tuberculosis. Early treatment with four anti-tubercular drugs (isoniazid, rifampicin, pyrazinamid, ethambutol) led to a rapid improvement of the patient's condition. The aim of this work is to provide a literature review to miliary tuberculosis infection in immunosuppressed CD patients, with the analysis of a clinical case report.

## **RESUMO**

A doença de Crohn é uma doença inflamatória intestinal caracterizada por uma resposta inflamatória inapropriada. A terapêutica com biológicos dirigidos a mediadores inflamatórios específicos revolucionou o tratamento mas aumentou a susceptibilidade a infecção ao induzir um nível de imunossupressão. Isto envolve infecção a agentes comuns mas também a possibilidade de tuberculose. Apresentamos o caso clínico de um doente com doença inflamatória intestinal que apesar do rastreio negativo, desenvolveu tuberculose miliar, enquanto realizava terapêutica imunossupressora dupla (azatioprina e infliximab) por doença de Crohn refratária. À admissão apresentava febre, perda ponderal, elevação das transaminases, coagulopatia, anemia e neutropenia. Os exames complementares de diagnóstico, que incluíram tomografia computadorizada, broncofibroscopia e biópsia hepática, confirmaram o diagnóstico de tuberculose miliar. O início precoce de terapêutica anti-tubercular quadrupla (isoniazida, rifampicina, pirazinamida, etambutol) permitiu uma rápida melhoria clínica do doente. O objectivo deste trabalho consiste em fornecer uma revisão da literatura sobre infecção por tuberculose miliar em doentes com doença de Crohn imunossuprimidos, com a análise de um caso clínico.

## BACKGROUND

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) inhibitors are established as standard treatment of several immune mediated inflammatory diseases such as CD. Infliximab is currently the most potent treatment to achieve clinical remission and mucosal healing in patients with CD refractory to conventional treatments, but represents an increased risk of opportunist infection, specially tuberculosis.

Screening and eventually preventive chemotherapy should become the standard of care for individuals undergoing TNF- $\alpha$  antagonist, specially if it is combined with other immunosuppressive therapy.

## CASE REPORT

A 40-year old caucasian man diagnosed with Crohn's disease since 2001, after presenting with bloody diarrhea and ferropenic anemia. At diagnosis time, disease had an ileocolonic location and a predominantly stenotic behavior, classified as A2L3B2 according to Montreal classification. Over the years the patient experienced disease activity and severity progression to dependence on steroids, reason for subsequent initiation of immunosuppression with azathioprine (AZA). Recently, last year, while on AZA maintenance therapy, he had developed a flare with an intestinal subocclusion episode, followed by a steroid-refractory course. During the in-stay, several immunoserologies were performed, as well as interferon-gamma released assays (IGRA), both negative. Anti-TNF- $\alpha$  was proposed and after a thorough questioning, two negative

tuberculin skin tests and a normal chest x-ray (Fig. 1), infliximab was started in June 2015 (induction followed by 5 mg/kg infusion every 8 week).

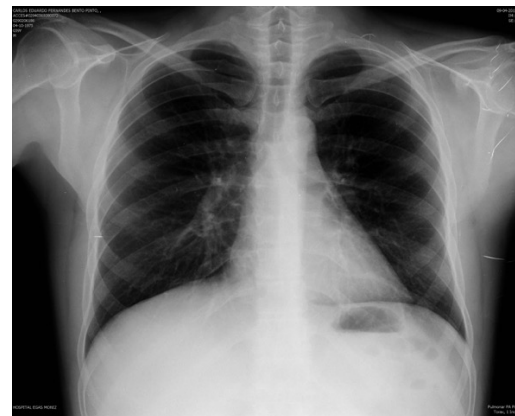


Fig. 1 – Normal chest x-ray performed before anti-TNF therapy.

Early August, he presented in ER with flu-like symptoms as cough, rhinorrhea, pleuritic pain, asthenia, intermittent fever (max 38°C) and non-selective anorexia. An x-ray showed no alterations and azitromycin was prescribed for a three-day course, with slight improvement of the patient's condition. He kept weight lost and due

to a new fever episode, he was observed by gastroenterology late September. Laboratory results performed at the time showed anemia (haemoglobin: 10.8 g/dL), leukopenia (1600/mm<sup>3</sup>), neutropenia (1120/mm<sup>3</sup>) and serum level of C-reactive protein of 4.5 mg/dL. Febril neutropenia was admitted and the patient was hospitalized. At admission he presented with fever (38°C), polypnea, without other respiratory symptoms and a 9 Kg weight lost (82-73 Kg). Clinical examination showed hepatomegaly. He had no skin alterations or palpable lymph nodes. Chest x-ray revealed diffuse interstitial infiltrate (Fig. 2).

All immunosuppressive therapies were immediately stopped and large spectrum antibiotics and support therapy initiated, unsuccessfully. One day after admission, there was no clinical improvement and he had

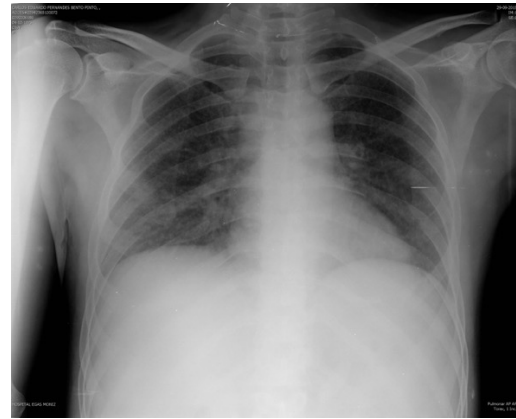


Fig. 2 – Chest x-ray showing diffuse interstitial infiltrate

worsening liver function tests and coagulopathy suggesting progressive hepatic cytolysis. CT imaging showed a bilateral and diffuse miliary pattern affecting the two lungs (Fig. 3a-b), except the lower segments of the lower lobes, compatible with miliary tuberculosis. There were also two irregular nodular condensations on the left lower lobe and left upper lobe, and mediastinal and para-tracheal enlarged lymph nodes.

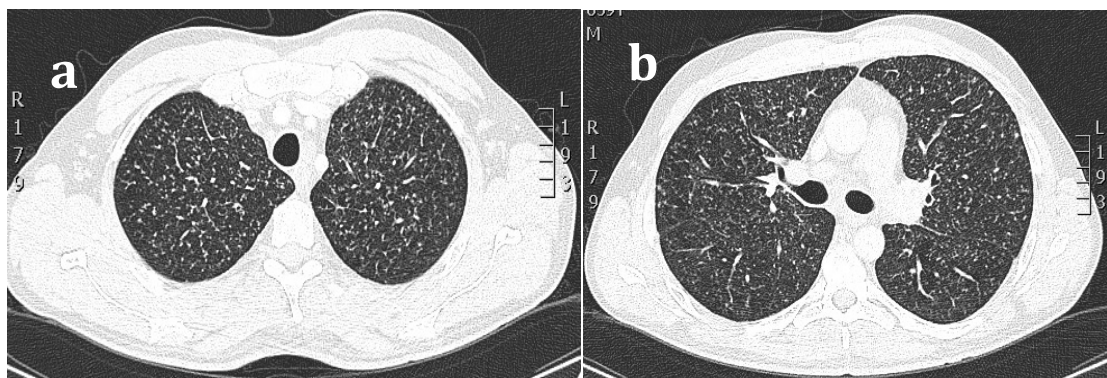


Fig. 3 – Chest CT imaging (a,b): bilateral and diffuse military pattern.

According to these findings, the suspicion of miliary tuberculosis in an immunosuppressed patient was high and, therefore, treatment was initiated with isoniazid 300 mg/day, rifampicin 600 mg/day, pyrazinamide 1500 mg/day and etambutol 1200 mg/day. To etiologic investigation, a hepatic biopsy was performed due to hepatomegaly and analytic abnormalities suggestive of hepatic cytolysis. The anatomopathologic exam reported granulomatous hepatitis (Fig. 4a-c) and acid-alcohol resistant bacillus (BAAR) search with Ziehl-Neelsen (Z-N) was positive (Fig. 4d). Bronchoscopic aspiration and bronchoalveolar lavage fluids were taken for microbiological tests. All

these test were negative for BAAR.

Iatrogenic febrile bicytopenia was admitted to be secondary to combined immunosuppression on a patient with miliary tuberculosis. The management was to continue anti-tubercular therapy and growth factor therapy, with GSF, was administered for three days with normalization of the absolute count of neutrophils.

The patient is still under treatment, with eleven months of anti-tubercular therapy left. Although CD treatment was stopped, he has a better health condition, the disease remained on remission and he had indication to re-initiate it after completing three months of anti-mycobacterium tuberculosis therapy.

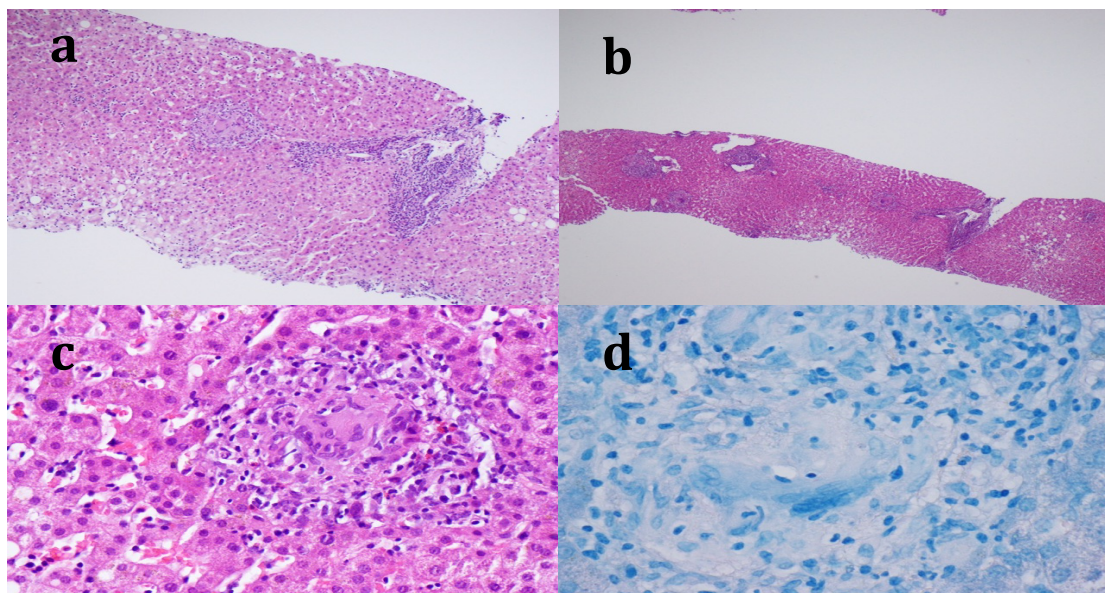


Fig. 4 – a: Photomicrograph showing tuberculous granuloma with Langhan giant multinucleated cell and lymphocytes palisade (H&E stain, x40); b: Photomicrograph showing portal space with lymphocytic infiltrate (H&E stain, x10); c: Photomicrograph showing intralobular granuloma (H&E stain, x60); d: Ziehl Neelsen stain: Koch's bacillus

## DISCUSSION

IBD is a chronic and disabling condition affecting millions of people in the world. The treatment algorithms and current guidelines result in a wider use of immunosuppressive and anti-TNF- $\alpha$  therapy in these patients.

Tuberculosis is also a prevalent disease, specially the latent form, which is considered an opportunistic infection (OI) in the presence of an immunosuppressive status.

The widespread use of anti TNF- $\alpha$  therapy, currently the most potent treatment to achieve clinical remission and mucosal healing in patients with Crohn's disease refractory to conventional treatments represents an increased risk of reactivation or development of primary tuberculosis. However, only a few cases of life-threatening disseminated tuberculosis have been reported <sup>(1, 2)</sup>.

Crohn's disease is a lifelong and relapsing disease arising from an interaction between genetic and environmental factors, difficult both to diagnose and to treat. The precise etiology is unknown but its characterized by an inappropriate inflammatory response and therefore the causal therapy is not yet available <sup>(3, 4)</sup>. Inductive therapy is followed by

therapy to keep remission <sup>(5)</sup>. Current therapeutic options are limited and comprise 5ASA, immunosuppressive and anti-TNF- $\alpha$ .

TNF- $\alpha$  has been identified as a crucial mediator of this abnormal immune response, and in recent years, biological therapies targeting TNF- $\alpha$ , like infliximab, have significantly improved the management of CD <sup>(4)</sup>.

TNF- $\alpha$  is a proinflammatory cytokine produced by activated macrophages in response to antigens such as *M. tuberculosis*, stimulating the differentiation of monocytes into macrophages, neutrophil recruitment and creation of granulomas. It is involved in both protection against *Mycobacter* and tuberculosis pathogenesis, being required for an effective immune response, for granuloma formation and to inhibit bacterial dissemination <sup>(2, 6)</sup>. Although inhibiting TNF- $\alpha$  reduces the inflammatory response in the setting of the inappropriate inflammatory response seen in CD, it may in turn reduce the effectiveness of the host immune system to mount a proper defense against infectious organisms. Patients with IBD should not be routinely considered to have altered immunocompetence per se, despite evidence of impaired innate mucosal

immunity.

Infliximab is a human murine chimeric monoclonal antibody with high binding affinity and specificity for TNF- $\alpha$ . It forms stable complexes with soluble and transmembrane forms of TNF- $\alpha$  and results in monocyte and macrophage lysis by cytotoxicity that depends on antibodies and complement<sup>(2)</sup>.

Soon after infliximab was introduced, large surveillance databases noted a significant increase in the incidence of TB. By 2001, 70 cases of disseminated TB had been reported in patients exposed to infliximab, with the time of diagnosis occurring at a median of 12 weeks after the initial exposure to infliximab, and after a median of 3 doses<sup>(6)</sup>. This finding supports the contention that the use of this TNF- $\alpha$  inhibitor is strongly associated with the reactivation of latent tuberculosis into secondary tuberculosis. The infliximab-associated cases had unusual characteristics that may have caused the TB infection to be especially severe.

Given the significant morbidity and mortality associated with TB reactivation, it is widely recommended the screening for evidence of latent TB. An incomplete screening could expose the patient to a severe, life

threatening and disseminated form of tuberculosis as described in this paper. A full clinical history and physical examination should be part of the initial assessment and all patients should have a chest radiography with either tuberculosis skin test (TST) or IGRA as investigations for latent infection. The widespread adoption of this mode of screening led to significant reductions in the incidence of TB reactivation in the setting of TNF- $\alpha$  inhibitor therapy. TST has some disadvantages: its specificity is low (there are false positive in vaccinated subjects or due to a booster effect), and its sensitivity is lower in immunosuppressed patients than in healthy subjects (some immunosuppressed patients may have false negative TST). Therefore patients with a negative tuberculin skin test but who have risk factors for previous TB exposure should be considered for a secondary highly specific TB test, such as IGRA that detects a rise in the serum IFN- $\gamma$  level following tuberculin exposure. IGRA can also be used for discrimination between anergy and true negative-antigen specific immune responses.

Preventive chemotherapy against tuberculosis should be offered to all individuals before beginning anti TNF-

$\alpha$  therapy whatever the underlying disease they are suffering from, in the presence of evidence of latent infection with *M. tuberculosis*. Preventive chemotherapy recommended is either 3 months of isoniazid plus rifampicin or isoniazid alone for 9 months. If isoniazid cannot be used, a preventive chemotherapy associating rifampicin and pyrazinamide for 2 months could be delivered. Anti TNF- $\alpha$  therapy can be started after an induction period of 3 weeks of preventive chemotherapy<sup>(2)</sup>. The treatment of disseminated forms of tuberculosis has some special features. It consists of four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months followed by 2 drugs (isoniazid, rifampicin) for at least 10 months. Clinician should be attentive to the complications of these prolonged treatments.

## CONCLUSION

Opportunistic infections are a major cause of death in Crohn's disease irrespective of comorbidity. The risk of infection appears to be related to immunosuppression and not due to disease itself <sup>(7)</sup>. The development of biologics is revolutionizing the treatment of immune-mediated inflammatory diseases such as CD. On

the other hand, this interception of inflammatory cytokines such as TNF- $\alpha$ , which are direct factors in the creation of inflammation, may restrain protective physiological reactions and cause reactions that can revive infectious diseases such as TB that are in dormancy <sup>(8)</sup>. An intensive surveillance and awareness of OI in CD patients requiring immunosuppressants should be performed, particularly for tuberculosis.

This case highlights the severity of tuberculosis acquired under TNF- $\alpha$  antagonist therapies and the importance of a complete screening for latent tuberculosis.

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